Infliximab in the treatment of pediatric Crohn's disease

Infliximab, a murine monoclonal antibody directed against TNF-α, has been approved for the induction and maintenance of remission in moderate-to-severe pediatric Crohn's disease that is unresponsive to conventional therapy. Infliximab is administered intravenously and can be infused over 2–3 h. The recommended induction dosing schedule consists of a series of three 5 mg/kg doses of infliximab delivered at weeks 0, 2 and 6. Regularly scheduled maintenance therapy is recommended to be given every 8 weeks. While initially it was believed that the administration of concomitant immunomodulators would significantly enhance the clinical efficacy of infliximab, recent data and safety concerns have called the benefit of such a strategy into question. Currently, clinical research on the use of infliximab in pediatric Crohn's disease has focused on the unmet need of being able to identify which patients could benefit most from infliximab therapy.

KEYWORDS: Crohn's disease, infliximab, pediatrics

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The inflammatory bowel diseases (IBD), commonly categorized as either Crohn's disease (CD) or ulcerative colitis, are immune-mediated conditions that result in chronic, relapsing inflammation primarily occurring within the gastrointestinal tract [1]. The phenotypes of CD that present in childhood have recently been recognized as being clinically aggressive and unique [2]. Appreciation of this clinical diversity has led to the goal of being able to stratify patients by risk of disease progression [3]. Until this goal is fully achieved, therapeutic decisions are currently made based upon the extent of disease and its clinical activity. A growing array of pharmacologic agents is available for use to achieve the induction and maintenance of remission in the pediatric IBD patient.

So-called conventional therapy was based on the use of corticosteroids for the induction of remission. 5′-aminosalicylic acid (5′-ASA) and perhaps antibiotics, were used for the maintenance of remission [4]. The main paradigm shift in treatment strategy over the past decade has been to base long-term therapy on the use of immunomodulators [5,6]. Most recently, this has included biologic therapies such as infliximab [7,8]. This paper will provide a brief overview of the structure, function and pharmacologic aspects of infliximab (**Box 1**). A clinical overview of its use in pediatric CD, including evidence for efficacy, various possible dosing strategies and safety issues, will then follow.

Infliximab: structure, function & pharmacodynamics

Infliximab is a murine, chimeric, high-molecular-weight (≈149 100 Da) monoclonal IgG antibody directed against human TNF-α. The structure of infliximab utilizes disulfide bonds to link a murine variable region (25%) to a human region (75%) [9]. Tumor necrosis factor is one of the key proinflammatory cytokines involved in the pathogenesis of chronic inflammatory bowel diseases, including both CD and ulcerative colitis [10].

Infliximab binds to soluble and membrane-bound TNF-α, which then leads to complement fixation and the apoptosis of TNF-producing activated T cells. Other potential mechanisms of action for infliximab include downregulation of other proinflammatory cytokines, decreased mucosal permeability, decreased acute-phase reactants, a reduction of lymphocyte and leukocyte migration and a reduction in endothelial adhesion factors [11].

Pharmacokinetics

Following an intravenous infusion, the serum half-life of infliximab is 10 days [9]. There is a dose-dependent maximum serum concentration (C_{max}) of infliximab. Elimination of infliximab is accomplished through degradation by nonspecific proteases rather than specific drug-metabolizing enzymes (i.e., cytochrome P450). A 5 mg/kg infusion will result in essentially undetectable (<0.1 μg/ml) serum infliximab

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Box 1. Pharmacology of infliximab.

Structure

- Chimeric, monoclonal IgG1 antibody to TNF composed of human constant and murine variable regions.

Mechanism of action

- Binds to soluble and membrane-bound TNF-α.

Pharmacodynamics

- Neutralizes soluble TNF-α and binds membrane-bound TNF-α which leads to the apoptosis of T cells and monocytes.

Pharmacokinetics

- C_{max} = 118 μg/ml, at a dose of 5 mg/kg after intravenous infusion. Complete serum clearance by 12 weeks with more rapid clearance in the presence of antibodies to infliximab.

Half-life

- 10 days.

Pediatric indication

- Moderate-to-severely active pediatric Crohn's disease refractory to conventional therapy.

levels by week 12. Most clinical trials of infliximab have been designed to investigate dosing every 8 weeks based on these pharmacokinetic properties of infliximab.

As a foreign protein, infliximab is immunogenic and antibodies to infliximab (ATI) have been shown to speed its clearance from the circulation leading to a decrease in its clinical efficacy and an increase in infusion reactions [12]. ATI formation has been shown to be impeded by the chronic administration of concomitant immunomodulators [13], premedication with corticosteroids prior to infliximab infusion [14] and by the regularly scheduled administration of infliximab itself [15].

Clinical efficacy of infliximab

Infliximab is approved for the treatment of moderate-to-severe pediatric CD that is unresponsive to conventional therapy. The approved dosing consists of administration in a controlled setting over 2–3 h as an intravenous infusion. The approved induction dose consists of three infusions of 5 mg/kg each that are delivered at 0, 2 and 6 weeks. Standard infliximab maintenance therapy is then given as a 5 mg/kg dose every 8 weeks. The use of infliximab for IBD began in pediatrics, as the first reported case of infliximab therapy in CD involved the treatment of a 13-year-old girl with severe Crohn's colitis [16].

Following approval of infliximab by the US FDA in 1998, its clinical efficacy as a maintenance agent in adult CD was established by double-blind, placebo-controlled trials. Maintenance treatment of active luminal CD was shown to be effective in A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen (ACCENT I). Published by Hanauer *et al.* in 2002 [17], this 54-week randomized controlled trial of 573 adult CD patients treated with infliximab for luminal disease demonstrated that 38.4% of CD patients who had received infliximab (10 mg/kg/dose) and 28.3% of those who had received infliximab (5 mg/kg/dose) every 8 weeks after induction were in remission as defined by a Crohn's Disease Activity Index (CDAI) of less than 150. In comparison, 13.6% of adult luminal CD patients who had received placebo were in remission at 54 weeks ($p = 0.007$).

The clinical efficacy of infliximab maintenance in treating adult CD patients with fistulizing disease was demonstrated in ACCENT II [18]. This study, published by Sands *et al.* in 2004, reported on 306 adult patients with fistulizing CD who were given a standard, three-dose induction course of infliximab. A total of 195 responders were then given maintenance therapy with placebo or infliximab (5 mg/kg) every 8 weeks. At 54 weeks, 36% of the patients who had received infliximab had no evidence of new active draining fistulas, as compared with 19% of those patients who had received placebo ($p = 0.009$).

A multicenter, open-label, dose-blinded trial conducted by Baldassano *et al.* suggested that infliximab may be safe and effective as short-term therapy of medically refractory moderate-to-severe CD in a pediatric population [19]. A total of 21 patients were enrolled and randomized to receive a single infusion of 1 mg/kg (n = 6), 5 mg/kg (n = 7) or 10 mg/kg (n = 8) over 2 h at week 0. The Pediatric Crohn's Disease Activity Index (PCDAI) was found to improve in 50 and 30% of the treated patients at weeks 2 and 12, respectively. There were no infusion reactions in any of the treatment arms.

De Ridder *et al.* demonstrated the efficacy of ongoing infliximab therapy in pediatric patients with refractory CD with and without fistulas [20]. Data was retrospectively reviewed, and yielded a total of 30 patients (aged 7–18 years) with refractory disease who were treated with up to 30 infusions (total 212 infusions). Mean follow-up was 25.3 months. Infliximab was effective in 53% of patients with refractory CD, with or without fistulas; however, approximately half of the patients became unresponsive to infliximab therapy. A total of six patients developed an allergic reaction

during infusion; in one patient, the allergic reaction occurred after an infliximab-free interval of 9 years. One patient died of sepsis.

The Randomized, Multi-center, Open-Label Study to Evaluate the Safety and Efficacy of Ant-TNF Monoclonal Antibody Remicade in Pediatric Subjects with Moderate to Severe Crohn's Disease (REACH) trial provided prospective data on the use of infliximab in the treatment of pediatric CD [21]. In this prospective, randomized clinical trial, patients (n = 112) with a PCDAI of more than 30 received standard infliximab (5 mg/kg) induction therapy at 0, 2 and 6 weeks. The 99 patients who responded to treatment at week 10 were then randomized to infliximab infusions (5 mg/kg) every 8 or 12 weeks through week 46. All patients included in this trial were on concurrent immunomodulator therapy. Clinical response was defined as a decrease in the PCDAI from baseline of greater than or equal to 15 points, and a total score of less than or equal to 30. Clinical remission was defined as a PCDAI of less than 10. This trial demonstrated a 10-week response rate of 88% and remission rate of 59%. At 54 weeks, patients who were receiving maintenance infliximab every 8 weeks demonstrated a 63.5% response rate and 55.8% remission rate. In contrast, for those who were receiving maintenance infliximab every 12 weeks, 33% were in response ($p = 0.002$) and 23.5% ($p < 0.001$) were in remission. The authors concluded that pediatric patients with moderate-to-severe CD demonstrated a high response rate to a three-dose induction regimen, and did better with an every-8-week rather than 12-week maintenance regimen.

The data from the REACH study served as a pivotal trial for infliximab to achieve regulatory approval in the Spring of 2006 as an agent for the induction and maintenance of remission in moderate-to-severe pediatric CD unresponsive to conventional therapy. How infliximab can best be utilized by pediatric CD patients still remains an open question. The next section will review the common dosing questions that are asked when using infliximab in this setting [21].

Episodic versus scheduled maintenance therapy

In the adult CD trial, ACCENT I [17], a subanalysis studied the impact of different treatment strategies (maintenance therapy versus 'on-demand') on mucosal healing, hospitalizations and surgeries. It was demonstrated that maintenance infusions every 8 weeks showed significantly higher healing rates achieved at 54 weeks (44%) as compared with episodic therapy (18%; $p = 0.026$) [22]. There were less hospitalizations in those patients treated with maintenance therapy (24 events per 100 patients) compared with CD patients treated episodically (38 per 100 patients; $p = 0.023$). A total of 3% of patients receiving maintenance therapy required intestinal surgery, compared with 7% of those treated episodically.

A recently published, multicenter, open label, prospective randomized trial also demonstrated the superiority of regularly scheduled maintenance therapy in severe pediatric CD. A total of 40 pediatric patients who became severely active despite being on an immunomodulator and corticosteroids were enrolled. A total of 34 of the 40 enrollees (85%) responded to standard induction therapy and were randomized to 1 year of episodic 'on-demand' dosing versus infliximab 5 mg/kg every 8 weeks. Relapse occurred in 23% of the regularly scheduled and 92% of the episodically dosed patients ($p < 0.003$). Also notable in this pediatric study was the effect on growth, with a statistically significant impact on mean growth velocity in the regularly scheduled (6.9 cm/year) versus the episodically dosed group (4.3 cm/year; $p = 0.01$) [23]. The authors concluded that there was a clear advantage to utilizing a regularly scheduled strategy rather than 'on-demand' dosing in pediatric CD patients.

Monotherapy versus concomitant immunosuppressives

It remains a clinical question whether infliximab therapy is best when given as monotherapy or in combination with concomitant immunomodulators. It has been shown that there may be direct drug–drug interactions that could affect efficacy. In 2003, Roblin *et al.* demonstrated that 6-thioguanine levels are enhanced by infliximab administration [24]. Additionally, Klotz *et al.* [9] point out an effect on infliximab serum levels and efficacy when administered with immunomodulator therapy. While thiopurines are the most common immunomodulator used in CD, methotrexate is the most common alternative [6]. The rheumatology literature has shown that trough serum infliximab levels are favorably affected by concomitant methotrexate use, and Vermeire *et al.* have shown that thiopurines as well as methotrexate can inhibit the formation of antibodies to infliximab (ATI) in CD patients [13].

Whether these effects translate into clinically meaningful differences remains controversial. Van Assche *et al.* reported a prospective trial in which adult CD patients who were receiving an immunomodulator were given induction and

then started on maintenance infliximab every 8 weeks. After 6 months, the patients were randomly assigned to continue or to withdraw concomitant immunosuppression after 6 months of therapy. Ultimately, there was no clinical or endoscopic difference between the two groups after 2 years, although serum trough levels of infliximab were higher in the immunomodulator group. Therefore, this study suggests that concomitant therapy beyond 6 months may not confer significant clinical advantage over infliximab monotherapy [25].

In a pediatric series, Kugathasan *et al.* further demonstrated that there was no clinical difference at 6 months amongst pediatric patients who had been receiving maintenance infliximab alone versus in combination with immunomodulators [26]. Full analysis of this study is not yet possible, as it is still only published in abstract. However, it should be highlighted that it includes immunomodulator withdrawal subjects similar to the design of Van Assche *et al.*

Such a withdrawal design is different than that used in the recently reported Study of Immunomodulator Naïve patients in Crohn's Disease (SONIC) trial [27]. Again, this study is still only published as an abstract and reports on an ongoing, prospective, multicenter study that includes 508 adult CD patients. All study patients were naïve to both biologics and immunomodulators, and were randomized into three groups receiving azathioprine, infliximab 5 mg/kg infusions or a combination of infliximab and azathioprine for 6 months. A total of 56.8% of the combination therapy and 44.4% of the infliximab monotherapy groups were in steroid-free remission at 6 months, compared with 30.6% of the azathioprine monotherapy group ($p < 0.001$ and $p < 0.009$, respectively). Most notably, the combination therapy group's steroid-free remission rate was statistically superior to the infliximab monotherapy group ($p = 0.022$).

The 1-year data from SONIC will help answer the now open question as to whether it is better to start infliximab with a concomitant immunomodulator and if so, how long to continue to do so. Certainly, long-term safety concerns would have to be balanced with the findings of SONIC, as combination therapy has been shown to increase the potential infectious and malignant risk of biologic therapy [28]. The potential risk of combination therapy may be especially important for the pediatric patient who may have many years on therapy and may also be at an increased risk for the rare but usually fatal hepatosplenic T-cell lymphoma (HSTCL), whose development has been associated with combination therapy [29,30].

Safety of infliximab treatment

As with all relatively new pharmacologic agents, the safety of long-term infliximab therapy is still under investigation. A listing of the most common, along with the less common side effects, appears in **Box 2**. This section will highlight the potential issues of infusion reactions, as well as infectious and malignancy-related concerns.

The earliest recognized adverse effects of infliximab were infusion reactions. Most are related to the immunogenic potential of infliximab, and include acute and delayed hypersensitivity reactions. Acute reactions can include symptoms of nausea and vomiting, headache, itching and urticaria, chest pain, dizziness, hemodynamic compromise and shortness of breath. Delayed infusion reactions are usually observed 2–12 days after treatment with infliximab. Delayed infusion reactions may occur after a single infusion or during maintenance treatment with infliximab, and symptoms may include: arthralgias, fever, peripheral edema, pruritus, headache, dysphagia and sore throat. It is now recognized that such reactions are more common with episodic than regularly scheduled maintenance therapy, and that ATI levels likely play a role [31]. The management of such reactions is well reviewed in the literature [32,33].

There is a growing literature on the issue of infusion reaction in pediatric inflammatory bowel patients. The REACH trial showed a 17–18% rate of infusion reactions in pediatric CD patients receiving regularly scheduled maintenance therapy, while more recent pediatric

Box 2. Adverse events associated with infliximab.

Common

- Acute infusion reaction (<17%)
- Delayed infusion reaction (<3%)
- Self-limited infections (e.g., upper respiratory infections)

Uncommon

- Reactivation of latent TB
- Bacterial infections including pneumonia
- Fungal infections
- Increase in aminotransferases
- Exacerbation of pre-existing demyelinating diseases
- Malignancy
- Contraindicated in uncompensated congestive heart failure

trials have shown a rate of 4% [23]. This rate is remarkably similar to the 3.6% rate of infusion reactions reported in the multicenter retrospective report by Jacobstein *et al.* [34]. In this report, 1652 infliximab infusions given to 243 pediatric inflammatory bowel patients at six centers were retrospectively reviewed. The authors specifically looked at the question of whether premedications prevented the development of infusion reactions. Premedications were defined as antipyretics, antihistamines or corticosteroids. The study found that premedications did not prevent patients from developing their first infusion reaction. However, premedications were effective at preventing a recurrence of an infusion reaction.

In addition to infusion reactions, an increased risk of infections has been reported in adult and pediatric patients who have received infliximab therapy. The REACH trial reported a 59.6% rate of infections [21]. The vast majority of these were uncomplicated upper respiratory infections. There were three cases of pneumonia (3%) and five reported abscesses (5%). Only one patient discontinued therapy due to bacterial infection. There were no fungal complications reported. It has also been observed that infliximab therapy increases the risk of reactivation of latent TB [35]. For this reason, the presence of latent or manifest TB must be ruled out before the first infusion. A purified protein derivative (PPD) skin test with or without concurrent recent chest x-ray is considered necessary before initiating treatment with infliximab [36].

There has been a long-standing concern that IBD, especially CD, confers an increased risk of lymphoma. In addition to the disease itself, the question has been raised whether the therapies used, specifically immunomodulators and biologic agents, increase the lymphoma risk. The earliest literature on this subject was based upon reports from tertiary referral centers. Since it is reasonable to assert that those who develop lymphoma in the presence of a chronic disease such as CD would preferentially be sent to a tertiary referral center for management, such studies were subject to significant bias [37]. Recognition of the potential bias in tertiary referral studies led to population-based studies. A Swedish study of more than 20,000 subjects demonstrated that CD patients may have a predilection to develop lymphoma at a younger age, but that any such risk ultimately becomes the same as the general population for older patients [38].

A recent meta-analysis looked specifically at the question of whether adult IBD patients on immunomodulatory therapy have an increased risk of lymphoma. The authors concluded that there was a fourfold increased risk of lymphoma in this patient population [39]. A similar finding in an abstract presented at Digestive Disease Week (DDW) 2008 from the Cancers Et Sur-risque Associé aux Maladies inflammatoires chroniques intestinales En France cohort (CESAME) study. This nationally based study of almost 21,000 French patients found a twofold increased risk of lymphoma in IBD patients. While only 35.3% of the patients had received immunomodulatory therapy, 13 of the 16 non-Hodgkin lymphomas identified were in patients who had received such therapy [40]. Therefore, there is now a clear evidence base to counsel patients that there is a two- to four-fold increased risk of lymphoma development in adult CD patients who have received immunomodulator therapy. The evidence at this time is strongest for the thiopurines. Long-term pediatric data on this issue does not exist at this time.

Regarding infliximab therapy and the risk of lymphoma, there is now an emerging literature looking at this issue. A meta-analysis was recently presented at DDW 2008 that looked at close to 9000 patients representing more than 18,000 patient-years. When using the Surveillance Epidemiology and End Results (SEER) database as a control, this study showed an incidence rate ratio (IRR) of 3.3 for patients who had received anti-TNF therapy. When comparing the anti-TNF group to immunomodulators alone, the IRR was 1.7 [41]. Clearly, a proportion of the anti-TNF-treated group had also received immunomodulators at some point in time, and the effect of this combination versus either agent alone remains an open question. Another question that still remains is to what degree severity of the underlying disease played a role, since patients enrolled in clinical trials are likely to be those who are most ill. Further study will need to be carried out to fully clarify the role of infliximab in this process, and this would be best performed in patients who have only received infliximab monotherapy.

Similar large cohort, long-term follow-up of pediatric CD patients receiving immunomodulatory and biologic agents are needed to fully establish the malignancy risk for pediatric Crohn's patients based upon therapies used. The FDA has recently placed anti-TNF therapies on a list of therapies that require further study to fully assess the pediatric cancer risk [101]. As a result, pediatric patients are being enrolled in a long-term safety registry. While these studies are still in process, a rare form of non-Hodgkin's

lymphoma has been reported in 15 pediatric and young adult patients who have been treated with infliximab and concomitant immunomodulators [29]. This cancer, HSTCL, currently lacks an effective therapy and has been seen in other immunosuppressed as well as immunocompetent patient populations [42]. Concern over this development has, in part, led some practitioners away from routinely using concomitant immunomodulators with infliximab [43]. Since all cases to date have involved thiopurines, the possibility of using methotrexate as an alternative immunomodulator has been explored [6,13]. It should be borne in mind that the idea that methotrexate would be less carcinogenic in this setting is not evidenced-based at this time. Further study will also be needed to answer the question of whether there are any environmental factors that may be contributing to the potential lymphoma risk. One potential environmental factor that has recently raised interest is the relatively high rate of exposure to diagnostic ionizing radiation in some CD patients [44].

Infliximab & pregnancy

Infliximab has category B pregnancy status. Large antibodies do not pass through the placenta during the first and second trimesters of pregnancy and, thus, the risk for fetal harm seems minimal [45]. However, in 2006, Vasiliauskas *et al.* published a case report showing evidence for transplacental transfer to the newborn of infliximab given to the mother. A 32-year-old woman with medically refractory CD had received five infusions of infliximab, the last one 2 weeks before delivery. A total of 6 weeks after delivery, the breast-fed infant's serum infliximab level was 39.5 µg/ml; infliximab was not detected in the breast milk. Serial measurements of the infant's infliximab levels decreased during the following 6 months, despite continuing with breastfeeding. [46]. Therefore, it seems prudent to try to avoid maintenance infusions during the last trimester if possible, because of the uncertainty that still exists. Data on the effects of infliximab on lactation are still forthcoming.

Conclusion

The therapeutic arsenal for pediatric CD is expanding. Infliximab has been shown to be an important addition to the list of agents used to treat this chronic autoinflammatory condition. While some patients are well served by conventional therapies, it has become clear that there are different phenotypes of CD, and that a significant number of patients have a clinical form that is poorly responsive to older treatment modalities. Many of these refractory patients can respond to infliximab. Additionally, the metabolic consequences of CD can be very effectively reversed with this agent allowing for normalization of linear growth. Deciding which patients should be started on infliximab and when to start the agent remains more clinical art than science at this time – but current research is striving to expand the evidence base.

Future perspective

Infliximab has ushered in the era of biologic therapy for pediatric CD. This therapeutic class has already grown to include additional monoclonal antibodies directed against TNF-α. These agents have demonstrated efficacy in adult patients, and pediatric experience with these agents is growing [47]. As with infliximab, it is likely that, in the near future, these agents will first be used in those pediatric patients with moderate-to-severe disease that is refractory to conventional therapy. Use of these agents is tempered by an appreciation of potential infectious and malignant complications. However, should ongoing studies demonstrate an enhanced safety profile that is not inferior

Executive summary

- Inflammatory bowel diseases (IBD) are chronic, relapsing conditions associated with autoinflammation primarily within the gastrointestinal tract.
- The use of conventional therapy in moderate-to-severely active inflammatory bowel diseases may not induce nor maintain remission.
- The proinflammatory cytokine TNF-α plays a key role in the pathogenesis of IBD.
- Infliximab is a murine, chimeric, monoclonal antibody directed against TNF-α and is capable of neutralizing this cytokine and downregulating the autoinflammatory cascade.
- Infliximab is the only biologic therapy currently approved for the treatment of moderate-to-severely active pediatric Crohn's disease refractory to conventional therapy. The induction sequence includes infusions at weeks 0, 2 and 6, followed by maintenance therapy with infusions every 8 weeks.
- Infliximab therapy is generally well tolerated. Both acute and delayed infusion reactions may occur; the risk of fungal and other infections and reactivation of latent TB is a concern; there may be a higher risk of developing malignancies, especially in those patients treated with concomitant immunomodulators.

to conventional therapy, the future could see the growing use of biologic agents as earlier and even first-line therapy.

Our expanding understanding of the pathogenesis of CD will lead to additional biologic therapies. Genetic and immunologic studies have identified a variety of defects in innate and adaptive immunity that result in different phenotypes of CD. Such genotype–phenotype characterizations will lead to an era of personalized treatment with therapeutic choices based upon an individual's own form of CD.

Financial & competing interests disclosure

Dr Joel Rosh discloses that he has received honoraria for speaking on behalf of of Abbott, Abbott Nutrition, Centocor, Prometheus and Shire. Dr Rosh has received research support from Abbott and Centocor and has served as a consultant to Abbott, Centocor, Millenium, Schering Plough and UCB. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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